

Survival advantage of patients on haemodiafiltration is independent of dialysis dose and patient characteristics: data from a single centre

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ABSTRACT

The benefit on line haemodiafiltration (HDF) confers on patient survival in the CKD population has been the subject of controversy due to the conflicting results from different studies.

On April 1 2005 all patients treated in a single centre were switched from high flux haemodialysis to on line HDF. This historical cohort study evaluated two nineteen-month periods – September 2003 to December 2006 – and included all the patients treated in this centre; 161 on HD and 168 on HDF.

Cox proportional hazards regression was used to assess the difference in mortality risk between treatment groups, adjusted for age, gender, four comorbid conditions (diabetes, coronary artery disease, cerebrovascular disease, peripheral vascular disease), dose of dialysis, serum calcium, LDL cholesterol, albumin and CRP.

Haemodiafiltration induced a significant decrease in serum calcium (9.2 ± 0.8 vs. 8.9 ± 0.7 ; $p=0.0005$) and LDL cholesterol (100.4 ± 33.3 vs. 86.6 ± 35.7 ; $p<0.003$).

Annual crude mortality rate decreased from 19.9 deaths/100 patient.years during the high-flux haemodialysis period to 8.9 deaths/100 patient.years during the HDF period.

The relative risk for all-cause mortality was significantly reduced by 98.5% for patients receiving HDF (HR 0.015; 95%CI 0.000 to 0.859).

This study shows a survival advantage of HDF which is independent of dialysis dose or patient characteristics and is largely due to a reduction in cardiovascular mortality. Because the interpretation of observational data is affected by residual confounding and selection bias, these data should be confirmed in a randomised trial.

Key-Words:

Dialysis patients; haemodiafiltration; mortality.

INTRODUCTION

In spite of steady improvement in haemodialysis technique and in the global treatment of dialysis patients over time, mortality rates among haemodialysis patients remain high, exceeding 20% per year¹. Data from the USRDS showed no improvement in the risk-adjusted mortality in the haemodialysis population over the last 15 years¹. Furthermore, data from the 2005 USRDS Annual Report indicate that risk-adjusted mortality for patients on dialysis over five

years has been increasing, rather than decreasing over time².

Cardiovascular disease is the major cause of death in the haemodialysis population. Chronic haemodialysis patients suffer from a high burden of cardiovascular disease which is only partially explained by the presence of traditional risk factors³, meaning other factors must be at play in the development of cardiovascular disease in this population. The retention of middle molecules (MM) has been associated with cardiovascular risk in chronic haemodialysis patients⁴. As MM are almost exclusively removed by convection, haemodiafiltration has become an attractive modality.

The benefit HDF confers on patient survival has long been the subject of controversy, however, as different studies yield conflicting results.

The aim of this study was to evaluate the impact on patient outcome of the switch from high-flux haemodialysis to on-line HDF in a population of CKD patients treated in a single centre.

PATIENTS AND METHODS

Study design

This was a survival cohort study which included all the patients treated in a single centre from September 1, 2003 to December 1, 2006. On April 1, 2005 all patients were switched from high-flux haemodialysis to on-line HDF, post dilution. All the patients treated in the unit had been on high-flux haemodialysis in the five years preceding the switch. 161 patients on haemodialysis and 168 patients on HDF were evaluated.

At the time of the switch, patients kept the same dialyser (high-flux polysulfone membrane) and the same blood flow. Dialysate flow was reduced in all patients by the use of an automatic device that keeps a constant blood:dialysate flow ratio of 1:1.2.

Substitution volume was automatically controlled during HDF by a device that uses an equation which is highly dependent on blood flow and takes the haematocrit, total plasma proteins and the ultrafiltration rate

during the session into account (Table I). With this device, all patients received less than 20 litres of substitution fluid per treatment.

Table I

Auto-substitution (equation)

$$Q_{sub} = Q_{sef} \times (1 - HCT/100) \times (1 - 7 \times TP/100) - Q_{uf}/60$$

Q_{sub}: Rate of substitution fluid (ml/min); **Q_{sef}**: Effective blood flow (ml/min); **HCT**: Haematocrit (%); **TP**: Total plasma proteins (g/dl); **Q_{uf}**: Ultrafiltration rate (ml/h)

Clinical and laboratory assessments

Data were obtained for all patients from medical record review and included demographic characteristics (age, gender, weight), blood pressure (systolic and diastolic BP values included the average of all pre-dialysis sessions' measurements during the last month of the evaluation periods), comorbid conditions (cardiac arrest, myocardial infarction, stroke, peripheral vascular disease, diabetes, anaemia, primary cause of ESRD), laboratory variables at the end of treatment periods (haemoglobin, transferrin saturation, ferritin, Kt/V urea, calcium, phosphate, parathormone, creatinine, albumin, CRP levels, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol), year of dialysis initiation, and dialysis modality.

Cohort characteristics

Patient characteristics by dialysis modality are presented in Table II. Age and time on renal replacement therapy were evaluated at the beginning of each treatment period. Dry weight, blood pressure, blood flow rate, dialysate flow rate and time of follow up were evaluated at the end of each treatment period. Patients receiving HDF showed higher systolic blood pressure than patients on haemodialysis. Table II shows that while blood flow rate was not changed at the time of the switch from HD to HDF, it was significantly higher in HDF patients at the end of treatment period. The use of the automatic device for control of dialysate flow rate meant patients treated by HDF had lower dialysate flow rate than patients on haemodialysis.

The cause of ESRD was quite similar in both treatment groups.

Table I

Cohort characteristics by dialysis modality

	HD	HDF	P
N° of patients	161	168	
Characteristics:			
Age (Yr)	66.1±13.3	63.7±14.6	NS
% male	54.7	51.8	NS
Dry weight (Kg)	61.1±12.6	63.2±13.6	NS
Time on RRT (months)	13.9±6.5	14.5±6.5	NS
Comorbid conditions:			
Diabetes (%)	18.6	23.2	NS
Myocardial infarction (%)	4.3	5.4	NS
Stroke (%)	14.3	10.1	NS
Peripheral vascular disease (%)	17.4	13.1	NS
%CVD	29.2	25.0	NS
Systolic BP (mm Hg)	130.8±24.7	137.5±20.4	0.007
Diastolic BP (mm Hg)	65.4±15.2	68.6±13.0	NS
MAP (mm Hg)	87.2±17.2	91.6±14.0	0.007
Time follow up (months)	13.9±6.5	14.5±6.5	NS
Blood flow (ml/min)	310.9±55.5	326.1±43.0	0,025
Dialysate flow (ml/min)	523.5±159.8	382.6±66.6	0.0005

Statistical analysis

Descriptive statistics characterised the study population. For independent samples, continuous and categorical variables were compared using the non-parametric two sample Kolmogorov Smirnov test and χ^2 test respectively. For paired samples, continuous and categorical variables were compared using the non-parametric Wilcoxon test and McNemar test respectively.

Life-table analyses were used to examine the estimated hazard function for patients who were captured in the census (all patients in the facility). In survival analysis we assessed differences in time to death and first hospitalisation. Patients were censored at death, loss to follow up (either because they received a kidney transplant or were transferred to another unit) or the end of the observation period; whichever came first. Overall patient survival was described using the Kaplan-Meier method based on dialysis modality.

A Cox proportional hazards regression model was used to generate crude and adjusted hazard ratios and 95% confidence intervals for the association between baseline patient characteristics and mortality or hospitalisation. The full model was adjusted for eleven covariates. A stepwise elimination selection method was performed. A chi-square was computed at each

step, and the variable was removed if the significance of its loss chi-square was greater than $p < 0.10$.

Analyses were conducted using SPSS 14.0.

RESULTS

A total of 161 patients on HD and 168 patients on HDF were evaluated. At the end of the evaluation period, patients on HDF showed higher Kt/V, higher albumin levels and lower CRP and serum calcium levels than patients receiving haemodialysis (Table III). HDF patients also showed lower levels of total and LDL cholesterol.

Table III

Patient characteristics by dialysis type

	HD	HDF	P
Serum urea (mg/dl)	137.8±35.2	131.5±37.6	NS
Kt/V	1.46±0.23	1.52±0.25	0.024
CRP (mg/dl)	1.88±3.87	1.11±1.72	0.028
Cholesterol (mg/dl)	184.1±45.8	166.7±40.8	0.001
Triglycerides (mg/dl)	171.6±101.6	162.2±85.7	NS
LDL cholesterol (mg/dl)	99.7±32.4	83.9±34.0	0.0005
HDL cholesterol (mg/dl)	48.2±11.7	50.5±14.8	NS
Creatinine (mg/dl)	8.5±2.2	8.4±2.4	NS
Albumin (mg/dl)	3.55±0.38	3.82±0.43	0.0005
Calcium (mg/dl)	9.2±0.8	8.5±0.7	0.0005
Phosphate (mg/dl)	4.9±1.7	4.8±1.6	NS

Paired analysis of some intermediate outcomes

Patients receiving both types of dialysis were analysed separately for some intermediate outcomes. This population included 115 individuals (Table IV).

Table IV

Paired analysis of patients characteristics and therapy-related factors: HDF versus haemodialysis

	HD	HDF	P
No. of patients	115	115	
Dry weight (Kg)	62.2±12.4	61.8±12.5	NS
Systolic BP (mm Hg)	133.5±22.8	135.4±20.4	NS
Diastolic BP (mm Hg)	66.3±13.6	67.9±13.9	NS
Time follow up (months)	15.6±5.6	17.4±4.3	0.006
Blood flow (ml/min)	319.6±50.9	325.6±47.3	NS
Dialysate flow (ml/min)	517.5±165.3	387.5±74.7	0.0005

After the switch to HDF, there were no changes in haemoglobin and haematocrit values and there were few biochemical changes, as can be seen in Table V. There was a significant increase in Kt/V urea despite a constant blood flow and a significant reduction in dialysate flow rate. Haemodiafiltration induced a significant decrease in serum calcium and total and LDL cholesterol, but no change in albumin or CRP levels (Table V).

Table V

Impact of HDF on patient characteristics (paired analysis)

	HD	HDF	P
Haemoglobin (mg/dl)	12.0±1.4	12.2±1.5	NS
Kt/V urea	1.50±0.24	1.61±0.24	0.0005
Calcium (mg/dl)	9.2±0.8	8.9±0.7	0.0005
Phosphate (mg/dl)	5.0±1.6	4.8±1.5	NS
Parathormone (ng/ml)	371.8±348.9	325.4±389.6	NS
Albumin (mg/dl)	3.99±0.40	3.95±0.44	NS
CRP (mg/dl)	1.14±1.58	1.15±1.95	NS
Total cholesterol (mg/dl)	183.7±43.5	168.7±42.4	0.009
Triglycerides (mg/dl)	171.2±99.1	161.8±79.6	NS
LDL cholesterol (mg/dl)	100.4±33.3	86.6±35.7	0.003
HDL cholesterol	48.5±11.6	50.4±16.2	NS

■ Crude mortality

Over the period of observation (September 2003 to November 2006), crude mortality rate decreased from 19.9 deaths/100 patient.years during the high-flux haemodialysis period to 8.9 deaths/100 patient.years during the HDF period. Annual mortality in the 10 years preceding the switch was between 16 and 20 deaths/100 patient.years.

The causes of mortality are shown in Table VI.

Table VI

Cause of mortality by type of dialysis (% of total)

	HD	HDF
Cardiac	36.4	10.9
Infection	10.9	7.3
Neoplasia	3.6	1.8
Malnutrition	12.7	12.7
Others	3.6	0

■ Relative risk for all-cause mortality

The relative risk for all-cause mortality after adjustments for age, gender, four comorbid conditions (diabetes, coronary artery disease, cerebrovascular disease, peripheral vascular disease), dose of dialysis, serum calcium, LDL cholesterol, albumin levels and CRP levels, was significantly reduced by 98.5% for patients receiving HDF. Dialysis modality interacted with gender (P=0.0005), and diabetes (P=0.009). These data are shown in Table VII.

Table VII

Risk factors for all-cause mortality

Variable	HR	95%CI	P
Age	1.031	0.999-1.063	0.058
Diabetes	3.026	0.981-9.333	0.054
LDL cholesterol	1.010	1.001-1.019	0.036
Calcium	1.045	1.019-1.072	0.001
Albumin	0.070	0.023-0.212	0.0005
CRP	1.069	0.999-1.143	0.052
Modality	0.015	0.000-0.859	0.042
Stroke	2.779	1.326-5.823	0.007

■ Relative risk for hospitalisation

The relative risk for hospitalisation was not significantly reduced for patients on HDF in comparison to patients on haemodialysis (adjusted for age, gender, four comorbid conditions, dose of dialysis, serum calcium, LDL cholesterol, albumin levels and CRP levels). The only predictors of hospitalisation were dose of dialysis (HR 0.437; CI95% 0.199 to 0.962), albumin levels (HR 0.889; CI95% 0.845 to 0.936) and the presence of cerebrovascular disease (HR 2.012; CI95% 1.278 to 3.167) or peripheral vascular disease (HR 2.319; CI95% 1.219 to 4.413).

■ DISCUSSION

This is the first study to show HDF has a greater beneficial effect on survival than haemodialysis, comparing two identical populations. The decrease in all-cause mortality was mainly due to a reduction in cardiovascular mortality.

Patients on HDF showed higher levels of albumin, lower CRP levels, lower levels of calcium, and lower total and LDL cholesterol. When patients receiving both types of dialysis were analysed separately, patients receiving HDF still had lower levels of serum calcium and lower total and LDL cholesterol. Predictors of all-cause mortality included higher serum calcium and LDL cholesterol levels, lower serum albumin, and a history of stroke.

Several studies showed an association between dialysis dose and survival. The National Cooperative Dialysis Study demonstrated the benefits of achieving a target Kt/V greater than 0.8, but showed no added benefit for Kt/V greater than 1^{5,6}. However, subsequent work has cast doubt on this threshold and suggested improved survival with increasing Kt/V^{7,8}. Consequently, most nephrologists have progressively increased the dose of dialysis.

Several epidemiological studies have suggested that dialysis with high-flux membranes could decrease mortality of haemodialysis patients. Over the world, nephrologists have increased the use of high-flux membranes. In 2004, 61% of all dialysers used worldwide contained a high-flux membrane and 93% of all dialysers used in the USA included a high-flux membrane⁹.

However, recent data from the HEMO study did not show any benefit from a higher dose of dialysis or the use of high-flux membranes. The HEMO study was a randomised clinical trial which included 1,846 patients undergoing thrice-weekly haemodialysis, and studied the effects of a higher dose of dialysis (equilibrated Kt/V higher than 1.2) and of the level of flux of the dialyser membrane on mortality. The results showed that the primary outcome, death from any cause, was not significantly influenced by the dose of dialysis or flux assignment: the relative risk of death in the high-flux group as compared with the low-flux group was 0.92 (95 percent confidence interval, 0.81 to 1.05; $P=0.23$)¹⁰.

The results of the HEMO study should not come as a surprise. In the USA, the maintenance of the risk-adjusted mortality for haemodialysis patients over the last fifteen years and the increased mortality of patients on haemodialysis for five or more years has paralleled a steady improvement in the delivered dose of dialysis over time and an increase in the use of

high-flux membranes. These data suggest that alternative therapies are needed to improve ESRD patient outcomes.

Haemodialysis patients suffer from a high burden of cardiovascular disease, the leading cause of death in this population. Data from the HEMO study showed that 40% of the patients had coronary heart disease, 19% had cerebrovascular disease and 23% had peripheral vascular disease³. However, traditional risk factors are insufficient to explain the high cardiovascular mortality of this population, meaning other factors such as the retention of uraemic toxins, especially the so-called middle molecules (MM), might be implicated in this adverse outcome⁴. As MMs are almost exclusively removed by convection, haemodiafiltration comes out as an attractive modality.

However, the superiority of HDF over haemodialysis on patient outcome is still a controversial issue. Recently, Rabindranath *et al.* performed a systematic review of randomised controlled trials (RCT) comparing haemodialysis and haemodiafiltration in the treatment of patients with end-stage renal disease to assess their clinical effectiveness¹¹. Regarding mortality, four studies were identified¹²⁻¹⁵ including a total of 326 patients. HDF was associated with significantly greater mortality risk than HD (relative risk 3.52; 95%CI 1.37 to 9.47). However, the authors concluded that the trials assessed were not powered adequately and had suboptimal method quality.

Jirka *et al.*¹⁶ evaluated HDF data from a large database of an international dialysis provider network. The study included 2,564 prevalent patients, 394 treated with HDF and 2,170 with haemodialysis, which were followed over a period of 12 months. Patients on HDF were heavier (67.9 versus 65.9 Kg, $P=0.03$) and longer on renal replacement therapy (6.61±4.94 versus 4.97±5.05 years, $P<0.001$). After adjustment for age, gender, co-morbidities, and time on renal replacement therapy, patients on HDF showed a significant 35.3% lower mortality risk than those treated by haemodialysis (HR 0.647; 95%CI 0.377-0.873).

In the Dialysis Outcomes and Practice Patterns Study (DOPPS), an observational study, outcomes were compared between patients receiving HDF and HD in five European countries. The study included 2,165 patients followed for 3 years. Patients receiving

HDF represented 11.7% and those receiving HD 88.3%. High-efficiency HDF patients had lower crude mortality rates than low-flux HD patients. After adjustments for patient characteristics and 14 co-morbid conditions, high-efficiency HDF patients had a significant 35% lower mortality risk than those receiving low-flux HD (relative risk 0.65; $P=0.01$)¹⁷.

There are now three observational studies showing a lower mortality risk for patients treated by HDF in comparison to patients on haemodialysis. However, this is the first study reporting a beneficial effect including two treatment groups which are quite similar in terms of number of patients and characteristics of the populations. Furthermore, it is the most robust study comparing the effect of haemodialysis versus HDF on several intermediate outcomes of the same population which are risk factors for mortality.

There are some limitations to our study. Firstly, this was not a prospective randomised study. Our analysis was retrospective of two sequential cohorts of dialysis patients. Clearly, a prospective randomised trial will need to be implemented to validate our findings. A second limitation is that a large proportion of the two cohorts included the same population (115 patients), meaning the survival advantage of patients on HDF could be due to selection of the best patients during the second period. However, the risk of selection bias is greatly reduced as the study included all the patients treated in the unit. Therefore, patients who died or were lost to follow up either because they received a kidney transplant or were transferred to another dialysis unit were replaced by the new patients that entered the unit. Furthermore, at the beginning of the treatment periods both treatment groups presented similar characteristics. It is a real world study comparing two consecutive periods in which mortality was significantly reduced after the initiation of HDF treatment. Noteworthy, mortality had been stabilised in the 10 years preceding the switch to HDF, and it decreased significantly afterwards in a sustained way. There is now a 19 month follow up period on HDF.

This study shows a beneficial effect of HDF that is not related to dialysis dose or patient characteristics and is mainly due to a reduction in cardiovascular mortality.

Conflict of interest statement. Dr Vinhas has received honoraria from Fresenius Medical Care.

References

- 1 USRDS. 2003 Annual Data Report.
- 2 USRDS. 2005 Annual Data Report
- 3 Cheung AK, Samak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, Teehan BP, Levey AS. Atherosclerotic cardiovascular disease risk factors in chronic haemodialysis patients. *Kidney Int* 2000; 58: 353-362
- 4 Vanholder R, Glorieux G, Lameire N. Uraemic toxins and cardiovascular disease. *Nephrol Dial Transpl* 2003; 18: 463-466
- 5 Harter HR. Review of significant findings from the National Cooperative Dialysis Study (NCDS). *Kidney Int* 1983; 23 [Suppl 3]: S107-S112
- 6 Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 1985; 28: 526-534
- 7 Charra B. Improving adequacy improves haemodialysis outcome. *EDTNA ERCA J* 2000; 26: 6-10
- 8 Parker T, Husni L, Huang W, Lew N, Lowrie E. Survival of haemodialysis patients in the United States is improved with greater quantity of dialysis. *Am J Kidney Dis* 1994; 23: 670-680
- 9 Grassmann A, Gioberge S, Moeller S, Brown G. ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends. *Nephrol Dial Transplant* 2005; 20: 2587-2593
- 10 Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance haemodialysis. *N Engl J Med* 2002; 347: 2010-2019
- 11 Rabindranath KS, Strippoli GFM, Roderick P, Wallace SA, MacLeod AM, Daly C. Comparison of hemodialysis, hemofiltration, and acetate-free biofiltration for ESRD: Systematic Review. *Am J Kidney Dis* 2005; 45: 437-447
- 12 Lin CL, Huang CC, Chang CT, et al. Clinical improvement by increased frequency of on-line haemodiafiltration. *Ren Fail* 2001;23:193-206
- 13 Locatelli F, Mastrangelo F, Redaelli B, et al. Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. *Kidney Int* 1996;50: 1293-1302
- 14 Teo KK, Basile C, Ulan RA, Hetherington MD, Kappagoda T. Effects of haemodialysis and hypertonic haemodiafiltration on cardiac function compared. *Kidney Int* 1987;32:399-407
- 15 Wizemann V, Lotz C, Techert F, Uthoff S. On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomized study. *Nephrol Dial Transplant* 2000;15 (Suppl 1): S43-S48
- 16 Jirka T, Cesare S, Di Benedetto A, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis. *Kidney Int* 2006;70:1524
- 17 Canaud B, Bragg-Gresham JL, Marshall MR, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney Int* 2006;69: 2087-2093

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